PATENT

#14 7/12

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Di Rienzo et al.

Serial No.: 09/251,274

Filed: February 16, 1999

For: METHODS FOR DETECTION OF PROMOTER POLYMORPHISM IN A UGT GENE PROMOTER

Group Art Unit: 1655

Examiner: A. Chakrabarti

Atty. Dkt. No.: ARCD:357US/DLP

CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

6/1/01
DATE

David L. Parker

DECLARATION UNDER RULE 131

Anna Di Rienza, Lalitha Iyer and Mark Ratain hereby declare as follows:

1. We are joint inventors of the subject matter disclosed and claimed in the above referenced patent application.

2. We understand that the U.S. Patent and Trademark Office Examiner handling the referenced application has taken the position that the Beutler et al. article appearing in Volume 95 of the Proceedings of the National Academy of Science, USA, pp. 8170-8174, July 1998, is relevant to the patentability of the referenced invention.

3. While we do not agree with the Examiner's conclusion in this regard, particularly with respect to certain aspects of our invention as set forth in the claims, we would point out that we made the subject invention, or at least as much of the subject invention as may be shown in the Beutler *et al.* article, in this country prior to July 1998. This is evidenced by the enclosed Abstract of our work from the March 30 - April 1, 1998 meeting of the American Society for Clinical Pharmacology and Therapeutics held in New Orleans, Louisiana. This Abstract is attached as Exhibit "A" hereto, and we refer you in particular to Abstract OII-B-3.

4. As can be seen from this Abstract, we discovered the existence and relevance of the two new alleles of the UGT promoter, the 5 [$(TA)_5$ TAA] and 8 [$(TA)_8$ TAA] alleles, and discovered that these promoter alleles appeared to be unique to populations of African origin. We further demonstrate that in contrast to previously identified other polymorphic alleles, allele five carriers (genotypes 5/6 and 5/7) showed higher levels of glucuronidation of bilirubin and SN-38, and that these results suggested the allele five resulted in an increase in UGT gene expression.

5. The data referred to in this Abstract was presented at the American Society for Clinical Pharmacology and Therapeutics meeting on March 30 - April 1, 1998 in New Orleans, Louisiana, and the Abstract reflecting this work was published prior to that time. We have attached a copy of the slides that were presented (Exhibit B). As can be seen from the slides, we fully presented a characterization of the allele 5 and allele 8, including a sequence analysis of each (see slide 6). Furthermore, an analysis of the rate of bilirubin glucuronidation was carried out on the allele 5 and allele 8 carriers (see slide 7). From this study, we demonstrated that carriers of allele 5 exhibited a bilirubin glucuronidation that was higher than that for the other genotypes, while the allele 8 carriers exhibited a glucuronidation level within the confidence levels of the allele 6 and allele 7 genotypes. Thus, this presentation demonstrates that we had discovered the allele 5 and allele 8, and made an initial assessment of their biologic significance, prior to July, 1998.

6. WE HEREBY DECLARE THAT ALL STATEMENTS MADE OF OUR OWN KNOWLEDGE ARE TRUE AND THAT ALL STATEMENTS MADE ON INFORMATION AND BELIEF ARE BELIEVED TO BE TRUE; AND FURTHER THAT THESE STATEMENTS WERE MADE WITH THE KNOWLEDGE THAT WILLFUL FALSE STATEMENTS AND THE LIKE SO MADE ARE PUNISHABLE BY FINE OR IMPRISONMENT, OR BOTH, UNDER SECTION 1001 OF TITLE 18 OF THE UNITED STATES CODE AND THAT SUCH WILLFUL FALSE STATEMENTS MAY JEOPARDIZE THE VALIDITY OF THE APPLICATION OR ANY PATENT ISSUED THEREON.

Anna Di Rienza — 5/31/01
Anna Di Rienza — Date

Lalitha Iyer — Date

Mark J. Ratain — Date

4. As can be seen from th[illegible] Abstract, we discovered the existence and relevance of the two new alleles of the UGT promot[illegible]r, the 5 [(TA)$_5$ TAA] and 8 [(TA)$_8$ TAA] alleles, and discovered that these promoter alleles app[illegible]ared to be unique to populations of African origin. We further demonstrate that in contrast to [illegible]reviously identified other polymorphic alleles, allele five carriers (genotypes 5/6 and 5/7) showe[illegible] higher levels of glucuronidation of bilirubin and SN-38, and that these results suggested the allel[illegible] five resulted in an <u>increase</u> in UGT gene expression.

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Anna Di Rienza — Date

Lalitha Iyer — May 31, 2001 — Date

Mark J. Ratain — Date

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_____ _____
Anna Di Rienza Date

_____ _____
Lalitha Iyer Date

_____ 5/31/01
Mark J. Ratain Date